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Original Articles

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GENERAL PATHOLOGY OF TUMORS OF ENDOCRINE GLANDS

*The First James Ewing Memorial Lecture**

HOWARD T. KARSNER

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THE notices which appeared in many scientific journals both here and abroad after the death of James Ewing make it unnecessary to itemize at this time his many accomplishments and the high honors bestowed on him. Nevertheless I cannot refrain from recounting some of my personal recollections. My acquaintance goes back to 1908, my friendship to 1911 and my devoted affection to 1918, dates which I consider noteworthy in my professional life.

Among many other tributes, James Ewing is the only man twice elected to the Council of the American Association of Pathologists and Bacteriologists. During the 14 years of that service, my post as secretary gave me the great privilege of close association with him and I was repeatedly a witness to a fine intellect at work on professional and administrative problems. Determined in learning basic facts, keen in analysis of them and logical in arrival at conclusions, he expressed himself

* Delivered at The New York Academy of Medicine, May 2, 1946.
From the Institute of Pathology, Western Reserve University and the University Hospitals of Cleveland.

with critical directness and conciseness, an example recalled with lasting admiration.

On many occasions I enjoyed and benefited by his hospitality, especially at the Memorial Hospital. No visit to New York was complete unless I had his aid in histopathological diagnosis, nor was I satisfied unless I had the opportunity to learn of advances in oncology presented with his background of great experience and profound wisdom. Without entering into details, I must say that I am proud of numerous kindnesses at his hands, proud that a great man would think well of me, proud that I had something to do with one of the honorary degrees conferred on him, and proud of his loyal friendship. His undaunted courage and distinguished achievements in the face of physical handicaps and personal tragedies, his utter devotion to his profession, his power of persuasion, his critical judgment, his ideals, his humor, his modesty, his integrity of character and his wholehearted humanness must always be an inspiration.

Never given to publication for its own sake and impatient with "pot-boilers," Ewing's interest in the dissemination of knowledge was continuous. He was by nature a teacher imbued with the belief that what he learned was well worth passing on to others. This was shown in the deep understanding and clarity so evident in his book and in his numerous papers. Although he never sought personal acclaim, he would have been much gratified by the establishment of a Memorial by his friends and admirers. Education and the improvement of knowledge by research were close to his heart. In my opinion, he would have been especially pleased by the allocation to a lectureship of part of the funds which have been contributed, regardless of whether the lectures are in the field in which he attained fame or in other branches of science. He himself took pleasure in the instruction of students, assistants and associates and he had that greatest of attributes of a teacher, enthusiasm. His name will be perpetuated by his work, but the lectures will refresh the stimulus so well provided by his life and career.

It is utterly impossible to express the sense of honor I feel in my selection to deliver the first of these memorial lectures. I am touched to the heart by this distinction because of my admiration and affection for James Ewing and because of my lasting gratitude to him. My contributions to the field of oncology are insignificant, but over the course of twenty years I have had an exceptional opportunity to learn about some

of the phenomena of tumors of endocrine glands. I welcome the privilege of conveying to you the result of these observations, not that they have intrinsic worth, but because they provoke thought and may stimulate further investigations in many channels.

Embryology. It is customary in discussion of neoplasia to consider the embryonal origin and development of the structures concerned. However, the newer investigations of embryology have led to abandonment of rigid interpretations of derivation from the three embryonal layers. On the basis of tridermal origins, many of the components of endocrine glands are evidently of epithelial nature. This appears to be true of hypophysis, thyroid, parathyroid, pancreas and adrenal medulla. The thymus is largely a mesoblastic derivative, but the cells of Hassall's corpuscles are epithelial in character regardless of their source. The adrenal cortex is probably a mesoblastic derivative but the morphology of the cells is epithelial and that is true of certain aspects of their behavior. Although the primitive sex-cells are derived from entoderm of the hind gut, yet the development of the mature gonad appears to represent a complex action of these epithelial cells and of mesoblast on each other, so that the final structure contains both components. This leads to certain difficulties in the interpretation of some of the tumors of ovary and testis. Furthermore, the approximation of certain anlagen may be of importance, as illustrated by the tumors in the sella turcica derived from Rathke's pouch. This may be exemplified also in tumors of ovary and testis composed of cells and structures which resemble those of adrenal cortex and the embryonal kidney. The anlagen of kidney and adrenal cortex lie in the genital ridge near that of the sex gland, and embryonal displacements or inclusions may possibly occur.

Genesis of the Tumors. It is generally agreed that two important factors are of significance, an intrinsic factor which evidently prepares the cell for neoplasia and a realization factor which brings it about. Heritable influences have not been clearly demonstrated in connection with tumors of endocrines and there has been no satisfactory explanation of other intrinsic factors. That hormones of one gland may lead to neoplasia in another is now undisputed and insofar as the affected gland is concerned, that is an extrinsic or realization factor. The lack of certain hormones may also be effective, probably because of release of inhibiting influences or because of disturbance of hormonal balance. That other extrinsic factors may operate is indicated by the experimental

irradiation of young mice, with the development in later life of ovarian tumors, which have now been shown to be true neoplasms.

Discussion still centers about the exact cells of origin, especially as to whether they are mature, embryonal or dedifferentiated. The tumors may contain cells which appear to be fully mature, as for example in the various forms of pituitary adenomas, the insular adenoma of the pancreas, and the cortical adenoma of the adrenal. These have tinctorial properties and cytoplasmic constituents like those of the adult organ. Conversely, however, morphological anaplasia is not infrequent as in the dysgerminoma of the ovary and the embryonal carcinoma of the testis.

An example of the controversies which may arise is the granulosa-cell tumor of the ovary. There are those who hold that this tumor is derived from mature cells of the granulosa; and this is based on human material and experimental observations. The intricacy of the reasoning is illustrated by the opinion that this tumor is derived from anovular nests of granulosa which persist in the mature organ. Although not yet settled, there is considerable doubt that granulosa will continue to exist without the presence of the ovum. An observation of a tiny granulosa-cell tumor in the hilum of the ovary where granulosa does not naturally occur led to the conclusion that the tumor could not have arisen in mature granulosa. Others believed that the granulosa-cell tumor is derived from nests of mesenchymal cells which subsequently differentiate in the course of neoplastic growth so as to resemble granulosa. Based on the same experimental material in the mouse, one group favored origin from mesenchyme but another believed that the tumors originate in germinal epithelium. Still other investigators, basing their view on experimental material of the same sort, ascribed the origin to undifferentiated parenchyma.

Another better known example is the tumor of the testis, called by some embryonal carcinoma and by others seminoma. Many adhere to the view that this lesion is the result of a one-sided development of a testicular teratoma and there is good evidence in support. There is no conclusive proof that the tumor is derived from seminal epithelium. The fact that many patients secrete chorionic gonadotrophin seems to point toward teratomatous origin.

Still another example is the so-called interstitial cell tumor of the testis. Although experimentally tumors of this sort have been induced,

yet there must still remain some question as to whether the cells of the tumor in man are derived from interstitial cells or from included rests of adrenal cortical cells. It is possible that assays of hormones in patients with these tumors may throw some light on derivation and nature. They have definite androgenic properties and if the androgens can be distinguished as of testicular or adrenal cortical origin in a sufficient number of cases, the situation may be clarified.

Even in those endocrine tumors which are composed of cells like those of the mature organ, no statement can be made as to whether they are derived from embryonal nests, mature cells or dedifferentiated cells.

Nature of the Tumors. Endocrine glands are subject to neoplastic growth derived from or resembling any of the constituent tissues. Thus there may be benign tumors of epithelial or connective tissue origin, carcinoma, sarcoma and various forms of mixed tumors and teratoid growths. These behave as do comparable tumors in other situations. Even here, there are occasional instances of peculiarities. Thus in the thyroid, adenomas and adenocarcinomas occur which are morphologically like those of other glands. However, the so-called metastasizing struma is peculiar in that the gland may show hyperplasia or adenoma in which no clear features of carcinoma are microscopically evident. Yet blood vessels are invaded and metastasis occurs.

Many of the tumors are derived from tissues which are of epithelial character or derivation. In the benign form these are usually called adenoma, even though they may have no acinic structure whatever. Examples are found in the various forms of adenoma of the pituitary and the cortical adenomas of the adrenal. The malignant forms, however, are called carcinoma without the prefix adeno. Other tumors which are evidently derived from cells of epithelial origin are not called adenoma or carcinoma. Thus the peculiar neoplasms of adrenal medulla are named pheochromocytoma, chromaffinoma, sympathicoma or ganglioneuroma, and the malignant forms by common custom are indicated by the suffix blastoma, as pheochromoblastoma or sympathicoblastoma. Then there are tumors the origin of which is so obscure that they are named according to type of cell. This is exemplified in the granulosa-cell tumor and the theca-cell tumor, or thecoma, of the ovary. There are still others in which the very character of the cells is far from clear. Here must be placed a tumor of the ovary composed of large cells with a lipid-containing vesicular cytoplasm, cells which morphologically re-

semble both cells of the adrenal cortex and of corpus luteum. These are sometimes called hypernephroid tumor, adrenal cortical adenoma, interrenaloma and have also been given the name masculinovoblastoma, a curious mixture of morphological and functional terminology.

Malignant tumors. As indicated above, many tumors of endocrines have the features common to tumors elsewhere which indicate whether they are malignant or non-malignant. There are others, however, in which this distinction is not altogether clear. The metastasizing struma is a case in point. The pituitary adenoma is usually localized in the gland or if large is confined by the capsule of the organ. Yet there are occasional instances in which capsule is penetrated and surrounding bone invaded. Thus the tumor has at least one important feature of malignant disease, namely invasion. However, it is usually impossible by microscopic examination of the tumor itself to detect a pattern of arrangement, pleomorphism of cells, abnormalities of mitotic figures or other features common to malignant tumors which would lead to a positive diagnosis. In some of the pheochromocytomas of the adrenal, pleomorphism is conspicuous, but the tumor is fully encapsulated, does not metastasize and does not recur after removal. Yet invasive tumors of this order will have microscopic features identical with the non-malignant form. Metastasis of some of the malignant tumors, such as the neuroblastoma of the adrenal or the carcinoma of the thyroid or the choriocarcinoma of the testis may be widespread, but certain other tumors, such as the malignant granulosa-cell tumor of the ovary, may show but little tendency to early or extensive metastasis.

Recurrence after removal poses a special question. Not long ago a pheochromocytoma of the adrenal was removed surgically in one of our clinics, but at operation a smaller tumor of identically the same nature was found near the renal pedicle. No answer can be given to the question as to whether this smaller mass was metastatic or originated in an aberrant medullary mass. The presence of supernumerary or aberrant adrenal tissue is well known and confuses the pathologist when he is confronted with the problem of metastasis, recurrence, or a new tumor in an accessory site.

Reports on granulosa-cell tumor of the ovary indicate recurrence in as much as 38 per cent of the cases. Whether this is actually recurrence or the development of a new tumor is an open question. If this tumor is actually derived from mesoblastic cell rests with the potentiality

of developing into cells with the morphology of granulosa, there is the distinct possibility that what is thought to be a recurrence is a new tumor derived from another cell rest. This is emphasized by the fact that granulosa-cell tumors have been found primarily in broad ligament and hilum of ovary. In order to be sure that there is recurrence, evidence must be adduced to show that the original tumor had malignant features. The difficulties in this direction have been indicated above. When penetration of capsule, direct invasion and metastasis are present, the diagnosis is unquestioned. Yet these may not be evident in a surgical specimen. As the result of a large experience, I have formed the opinion that in many of the peculiar tumors of endocrine glands, the most distinctive feature of malignant disease is invasion of the capsule rather than alterations of cytology. Before accepting a diagnosis of recurrence, I would wish to have clear indications of malignant disease in the original tumor.

Thus it is evident that percentages of benign and malignant forms of several of the tumors of endocrines must be determined by critical analysis of all the facts available.

Place of Function in Identification. Although some of the tumors of other glands may exhibit function of a sort, as in mammary neoplasms, yet special forms of tumors of endocrines display functional activities which are identical with or closely simulate those of the gland from which the tumor is derived. This necessarily brings the oncologist into the field of endocrinology. However, he recognizes that just as there are unexplored areas of oncology, so there is much yet to be learned about endocrinology. Internal secretions are subject to metabolic changes, and what is recovered in the blood or urine is not necessarily the exact substance produced by the gland. Methods of assay have been vastly improved, but the techniques for the most part are as esoteric as the field itself. Simplification without loss of precision, and even improved accuracy, are essential to more widespread use. Furthermore, the entire series of chemical changes up to the point of excretion must be understood. Complete knowledge of these factors provides the only satisfactory explanation of functioning endocrine tumors.

The content of hormone in a given tumor may give a clew as to its activity, but there remain the questions as to whether the tumor secretes a normal hormone in excess, whether the hormone is in its original form, whether the material extracted represents formative constituents for

production of normal hormones, whether there is a pattern of constituents which may be significant, and whether the tumor serves principally as a storage place. Extractions from tumors often yield such minute amounts of steroids or hormones that distribution of fractions cannot be determined. The use of autopsy material is limited by the fact that by the time of death what appeared originally to be disease of one gland has usually become polyglandular.

Thus the most productive studies are those made during the life of the patient. Yet even so, the tumor must be identified morphologically. There are instances in which morphological diagnosis is difficult or even impossible. What then can be done? It seems like arguing in a circle to say that a tumor devoid of specific morphological characterization belongs in a certain group because it has exhibited the functional effects ascribed to that group. Exact information cannot be collected or analyzed on that basis. It were better to leave such tumors unclassified than to read into them interpretations which are largely hypothetical. Although it must be admitted that certain clinical complexes with definite functional manifestations, as for example some of the disorders of cardiac conduction, cannot be given a clear cut morphological background, yet it is certain that most diseases have an identifying morbid anatomy. This serves both pathological and experimental investigations. The disease induced in animals must closely resemble that of man, if satisfactory deductions are to be drawn. There is no good reason why this does not apply to functional endocrine tumors, and much of what follows is based on that premise.

Morphology. The functional tumors may be incorporated in a gland without either encapsulation or pressure effects on the rest of the organ. This is particularly true of some of the pituitary adenomas. In such an instance, however, the question often arises as to whether the lesion is a localized hyperplasia or a neoplasm. Usually this question is resolved only by the personal opinion of the observer. However, when the growth replaces the entire pituitary and attains such size as to produce enlargement of the sella turcica, there is no dispute, but even in these instances there may be a surrounding rim of non-neoplastic cells. When the lesion is definitely nodular, morphologists generally agree that it is neoplastic, as for example, the thyroid adenoma, but functional studies may not entirely support this view.

Other tumors may grow in part of a gland and displace other parts.

Thus the cortical adenoma of the adrenal may be partly surrounded by other parts of the cortex and the medullary pheochromocytoma similarly partly surrounded. And this is true of these tumors even when they have a diameter of several centimeters.

The shape of the tumors is generally spherical, but as elsewhere, the configuration of the organ or the influence of surrounding structures may modify the form. As a rule the outer surface is smooth, but there are curious exceptions. Tumors of pituitary, of thymus, of parathyroid, of adrenal and of testis usually have a smooth surface. The granulosa-cell tumor of the ovary when small may be smooth but the larger tumor is nodular. Yet the theca-cell tumor of the ovary usually has a smooth surface. Testicular tubular adenoma of the ovary is usually nodular, but sarcomatoid and mixed forms of arrhenoblastoma have a smooth surface.

The capsule of these tumors is usually the capsule of the gland rather than one stimulated by the presence of the tumor. A noteworthy exception is the thyroid adenoma.

Cytology has been commented on in reference to malignant character. The cells may be uniform and resemble those of the mature gland, but departures are frequent. Pleomorphism and active mitosis may occur in tumors which do not behave as malignant neoplasms. Thus, as has been said above, it is often impossible on the basis of cellular form or arrangement to distinguish between benign and malignant forms.

Just as ductless glands are richly vascularized, so are most of the tumors of these organs. There are of course wide variations in this respect, but the adrenal tumors are noteworthy for plentiful blood vessels. Although not uniformly true, the malignant tumors are generally more richly vascularized than the benign forms. The blood vessels are small and for the most part of capillary size. Occasionally there are large vascular spaces lined only by endothelium. Consequently some of the tumors may exhibit hemorrhage and necrosis, and subsequent hematogenous pigmentation. Naked unlined vascular slits may occasionally be observed but have little significance as an indication of malignant character. There is no clear indication that the tumors accompanied by hormonal disturbance are more richly vascularized than are others.

Chemical components. These have not been studied extensively. Attention, however, has been paid to lipid content of the cells of certain of the tumors, without throwing great light on their origin. Certainly exact chemical analysis is to be preferred above histo-chemical tech-

niques. Attempts have been made to distinguish between the lipid content of the granulosa-cell tumor and the thecoma of the ovary but no truly significant differences have been disclosed. The study of the lipid content of cortical adrenal tumors and of the so-called interstitial cell tumors of the testis has given no satisfactory information. Even if the lipid content of the normal human adrenal were definitely known, there is no assurance that neoplastic cells of that gland would be chemically identical. Nevertheless, further studies may ultimately throw some light on the nature and probable origin of some of the functional endocrine tumors. No special information has been obtained by examinations for glycogen. Thyroid tumors have been found to contain iodin and thyroxin in amounts approximating those of the active gland.

Content of hormones. Certain insular tumors of the pancreas, including adenoma, carcinoma and its metastases, contain a substance which behaves as does insulin and the clinical manifestations are not distinguishable from those of hyperinsulinism. That these neoplastic cells produce an insulin exactly identical with that elaborated by the normal islet cells has not yet been established. With an adequate amount of tissue it should be possible to isolate the hormone in crystalline form. Then a statement could be made as to whether the neoplastic cells produce true insulin.

Medullary tumors of the adrenal contain adrenalin and probably produce it, and the pressor substance discovered in the blood of the patients with spasmodic hypertension behaves pharmacologically as does adrenalin.

Estrogenic and androgenic substances have not been identified in the cortical adrenal tumors, even though androgenic substance has been demonstrated in the urine of patients with virilizing tumors or with cortical hyperplasia.

Granulosa-cell tumors of the ovary have been shown to contain estrogenic substance in amounts equal to or greater than is true of the ovary, but this has not been proved to be alpha estradiol.

The content of thyroxin in thyroid tumors has been mentioned without maintaining that this is the one effective hormone of the thyroid.

None of these observations has yet established positively whether the tumor elaborates the hormone or is simply a place of storage, but the former seems likely. In certain measure, however, the same may be

said of the non-tumorous gland.

Tinctorial Properties of Cells. Chromophobe adenomas of the pituitary produce signs and symptoms because of their mass. The same may be true of acidophilic and basophilic adenomas. In addition, however, the acidophilic adenomas are commonly associated with acromegaly. Thus it is assumed that the acidophilic cells produce the growth promoting hormone of the gland. There are rare instances of acromegaly in which the adenoma is not acidophilic. This is explained by the statement that the cells have become so exhausted that they no longer take the acid stain, which may well be true. There is no conclusive proof of the explanation and doubt is thrown on the complete validity of the original assumption. Of course, improper fixation and faults in staining technique may be responsible, but that statement also begs the issue. It is conceivable, however, that cells originally acidophilic may, when they undergo neoplastic proliferation, lose their tinctorial peculiarity without alteration of their functional capacity. Furthermore, if as has been suggested, the chromophobe cell is the precursor of the acidophilic and basophilic cells, an adenoma, not acidophilic, may perhaps be looked upon as made up of immature cells without fulfillment of potential morphological differentiation but with the functional capacity of the mature cell.

Basophilic adenomas of the pituitary are commonly associated with Cushing's disease, but there are instances of the disease in which no such adenoma is found. Much more uniform is the coincidence of cortical hyperplasia of the adrenals. In one of our cases, the cortical hyperplasia was extreme and only by serial section was a tiny clump of basophilic cells discovered in the pituitary. This was so small that reasonable question was raised as to whether it was a focal hyperplasia or a neoplasm. A recent study points toward the view that Cushing's disease is the result of functional disturbance of the hypothalamic region and that the basophilic adenoma when present, even with the hyalinization of cytoplasm of basophilic cells, the so-called Crooke change, is secondary, as is probably true of the cortical adrenal hyperplasia.

There is ample evidence of the fact that the production of insulin is governed by the beta cells, yet the insular tumors of the pancreas may contain but few cells with characteristic beta granules. The question then arises as to whether the cells which constitute most of the tumor are derivatives of original beta cells, morphologically altered in

the course of neoplastic proliferation, whether they originate in other insular cells which have assumed new function, or whether they are a new race.

It has been claimed that cortical tumors of the adrenal, accompanied by virilization, contain cells peculiar in their affinity for fuchsin, the so-called fuchsinophile cells, and there is no doubt that such cells exist. The interpretation that they deal with virilization, however, is not sufficiently well founded. The staining technique can be manipulated so as to show these cells in the common non-functional adenomas of the adrenal cortex and indeed in medullary tumors, as well as in other organs of the body. At least, the association of fuchsinophile cells and virilization is not proved.

Physiological Manifestations. The effects of the functional tumors of the endocrines are necessarily related to their production of hormones, natural or altered, but it is not necessary to assume that these act directly upon other endocrines or upon other tissues or organs. It may be that in many instances the effects depend upon alterations of the internal environment of the body. In this sense, certain glands may act as synergists or antagonists. Ovary and adrenal cortex are said to be synergists. If this be so, hyperfunction of the ovary, as mimicked by prolonged injections of estrogens, may lead to brown degeneration of the adrenal cortex, probably a manifestation of hypofunction of adrenal cortex, whereas inhibition of ovarian secretion by ablation is often followed by nodular hyperplasia of the adrenal cortex, probably as an index of hyperfunction. The former effect may well be due to direct effect of estrogens, whilst the latter is probably the result of an alteration of internal environment. It must be said, however, that this example is not accepted by all endocrinologists and that the principal examples of synergism are to be found in certain internal secretions of the pituitary, e.g., the two gonadotrophins. An example of antagonists is to be found in pancreatic islets and adrenal medulla. Active function of the latter raises blood sugar, but insulin lowers it. Lowering of the blood sugar by insulin stimulates the adrenal medulla, but this stimulus is due to the blood sugar level, an alteration of internal environment, rather than directly to insulin.

There must also be involved a state or condition of receptors for hormones or receptors for the stimulus of altered internal environment. This appears to be illustrated in the statement that acidophilic adenoma

of the pituitary is accompanied by gigantism if it occurs in early life and by acromegaly if in later life. The importance of the state of receptors is probably a general principle of endocrinology as witnessed also in such manifestations as unilateral exophthalmos in Graves' disease and in the occurrence of unilateral gynecomastia.

As said above, the products found in blood and urine are not necessarily the exact hormones produced by the glands. All these facts must be recalled in any interpretation of clinical phenomena.

Virilization. This is broadly interpreted to mean sexual precocity in males and the appearance of certain masculine characters in females. In connection with the latter it must be recognized that some women are hairy, broad shouldered and have deep voices, evidently on the basis of constitution and heredity. It is a mistake to assume that they harbor virilizing tumors, although it must be admitted that the features may be due to endocrine disturbance.

Precocity in boys may accompany cortical adrenal tumors and the so-called interstitial-cell tumors of the testis. The boys are above average stature and have an advanced bone-age and mental age. The face is mature in appearance and the voice deep. Sometimes the boys have a slight beard. Hair grows in axilla and on the chest, and a male escutcheon appears. The external genitalia are large and erections are more frequent than would be expected for the age. Although it has been said that ejaculations containing spermatozoa have been observed, this seems unlikely, because if there is an excess of male sex hormone, spermatogenesis should be depressed.

Virilization of females occurs in children, in young women, and in some measure in older women. It is an accompaniment of cortical adrenal tumors and of tumors of the ovary especially the arrhenoblastoma and the so-called hypernephroid tumors. The clinical features in children include those of the so-called adreno-genital syndrome, such as broad shoulders, narrow hips, growth of hair in axilla and on pubis, prominent mons veneris and large clitoris. Musculature is well developed and in these cases, as in the precocious boys, the figure is indicated by the term "infant Hercules." The voice is sometimes deep.

In young women, after the menarche, the physical signs described above as occurring in children are much the same but may be noted as a distinct change from previous feminine characters. Included also is amenorrhea. Natural libido may be preserved, may be absent, or is said

in some cases to be inverted. In women past the menopause, the principal manifestation is hirsutism, which may be accompanied by deep voice and enlarged clitoris.

In children, the tumor is usually the cortical adrenal tumor. In young women it may be either that tumor or one of the ovarian neoplasms. In older women, it is frequently the hypernephroid tumor of the ovary.

Feminization. This term is only relative and subject to wide interpretation. It may be taken to include precocity in girls, acquisition of female characters in sexually immature adult females, so-called rejuvenation in women in post-menstrual life, and the production of certain somatic changes in males.

Sexual precocity in female children is well illustrated by the effects of the granulosa-cell tumor of the ovary. The child may show increased stature, but the more striking change is in the bodily configuration with broad hips, long fingernails, enlarged breasts, growth of hair on pubis, large mons veneris and large clitoris. Associated is periodic uterine bleeding, usually scanty, lasting a day or two and recurring every three or four weeks. In order to interpret these features as those of premature sexual development in the true sense it would be necessary to have ovulation with the flow. Ovulation has not been proven and is unlikely if there is an excess of estrogenic substance in the blood. By investigation of human subjects and experimental animals there is little doubt that there is an alteration of internal environment due to production of estrogenic substance by the tumor.

However, similar changes may be observed with cortical adrenal tumors, with pituitary tumors, with alteration of pituitary function and with lesions of the hypothalamic region. Also, it must be recalled that in most cases of precocity no tumor or other organic basis is found.

Women of post-menopausal years are said to be rejuvenated, but this term is literally incorrect. The principal phenomenon is irregularly periodic or continuous uterine bleeding. The atrophic ovary cannot produce ova and the bleeding is necessarily anovulatory. The patients do not regularly show psychic or other manifestations of a return of sexual life. The associated tumor is usually the granulosa-cell tumor of the ovary.

Rarely women attain adult life with none of the primary or secondary sex characters. This may be due to hypophyseal dysfunction or absence or failure of development of ovaries. In one instance, a woman

30 years old developed a choriocarcinoma in the pelvis, exact origin not determined, and then had enlargement of breasts, growth of pubic and axillary hair, and irregularly periodic but slight uterine bleeding. Postmortem examination of the pelvic organs disclosed no ovaries and the bleeding must have been anovulatory. There was an increased output of chorionic gonadotrophin and of estrogen with suggestive increase in pregnanediol, but no increase in 17-ketosteroids. Thus the somatic changes are explained. Other comparable cases have been reported but without the assay of hormones.

So-called feminization in males is rather a reduction in maleness than a sexual inversion. The principal changes are atrophy of testes, reduction or absence of libido and gynecomastia. These have been described in two cases of cortical adrenal tumor and are frequent in cases of choriocarcinoma, either in testis or in extragenital position. In a few cases, assays have shown increases in chorionic gonadotrophin and of estrogens. Of interest is the fact that the gynecomastia is usually bilateral, in contrast to the frequency of unilateral gynecomastia in cases without obvious endocrine changes.

Blood pressure. Changes in blood pressure are usually accompanied by other phenomena. Thus, with the spasmodic hypertension observed with tumors of the adrenal medulla, usually not malignant, there are often headache, dyspnea, nausea and vomiting, vasomotor phenomena, glycosuria and collapse. These correspond to the phenomena produced by overdosage of adrenalin. Thus it may well be assumed that at intervals there is an increased output of adrenalin by the tumor. Occasional instances of continuous hypertension have been reported. This might well be due to liberation of adrenalin, in the sense of a continuous infusion. Although repetition of effective doses in experimental animals is followed by reduced elevation of blood pressure, this phenomenon is not observed if the doses are minute as would be true in infusions over a long period. In some of these cases, the persistent hypertension may be incidental.

Persistent hypertension occurs in patients with Cushing's disease, but as indicated above, the basophilic adenoma of the pituitary has not been conclusively shown to be the primary event. In some instances, acute and chronic arteriolar disease has been found in the kidneys, but this is by no means regular and cannot explain all cases. It occurs frequently with adrenal cortical tumors, probably due to excessive production of

steroids. Although experimentally desoxycorticosterone acetate will produce elevation of blood pressure, it has yet to be shown whether desoxycorticosterone or some other steroid operates in the tumor cases.

Metabolism. Increased basal metabolic rate accompanies certain adenomas and some of the carcinomas of the thyroid and is evidently due to production in excess of thyroid hormone. There is some dispute, however, as to whether this increased production is solely by the tumor or by the gland as a whole.

Certainly the metabolism of sugar is altered by the activity of certain adenomas and carcinomas of the pancreatic islets. Depression of insular function may occur with other tumors. Diabetes is a frequent accompaniment of tumors of the pituitary, of Cushing's disease and of tumors of adrenal cortex. The temporary glycosuria which may be associated with paroxysms due to pheochromocytoma is not a true diabetes.

Fat metabolism may be altered in both directions. The loss of fat in hyperthyroidism appears to be due to increased metabolic rate rather than to direct effects of the hormone. Obesity occurs in connection with adrenal cortical tumors and some of the ovarian tumors. Dystrophia adiposogenitalis (Fröhlich's syndrome) may sometimes be associated with tumors, but this is not always true. What part hormones play is somewhat uncertain, but the removal of virilizing tumors in young women is followed by deposit of fat in breasts and about hips. It has been shown that the fat deposits can be utilized in metabolism as in other fat. Although patients with Cushing's disease may appear to be obese, as exemplified in the "moon face," there is a mass of opinion to the effect that edema plays a larger part than accumulation of fat. As with other people, patients with endocrine tumors may become obese because of overeating and lack of exercise.

Protein metabolism. In hyperthyroid states, such as may accompany thyroid tumors, there is an increased destruction of proteins as indicated by augmented excretion of nitrogenous products in the urine. In certain diseases in which diabetes is part of the picture, protein may be utilized in the production of glucose. This gluconeogensis may be responsible for loss of cutaneous resiliency and the occurrence of abdominal striae and cutis marmorata in Cushing's disease. Perhaps muscular weakness may have the same cause. It has been called upon to explain osteoporosis and certain other phenomena.

Electrolytes. In occasional cases of Cushing's disease, chloride and potassium are affected, but there is no regularity as to increase or decrease. The importance of tumors of the parathyroids to calcium and phosphorus metabolism is well known. Experimental evidence indicates that these changes are due to the hormone of the parathyroids and that the changes in bones and the formation of renal calculi are the result of the concomitant alterations of internal environment.

Growth. As has been mentioned, growth is promoted by pituitary tumors, especially the acidophilic adenoma, by some of the cortical adrenal tumors of early life and perhaps by ovarian tumors in childhood. Experimental investigations of the effects of various hormones sometimes yield contradictory results and show variations in different species. Thus there is difficulty in applying these studies to man. There is probably a considerable interplay on the part of different glands and a synergism of different hormones of the same gland, as for example, the pituitary. Thus it is said that the growth hormone of the pituitary is favorably influenced by other secretions of the pituitary. In addition there are probably also genetic factors of significance.

Concluding Comment. Endocrine glands may be the seat of primary and metastatic tumors such as occur in other structures, but in addition there is a relatively small number of neoplasms of these glands which display striking functional activity. In the sense that hormones are soluble products of specialized tissue, which through the circulation affect other tissues, the tumors undoubtedly produce hormones, but in many instances there is no proof that these are identical with hormones produced by the normal gland. The clinical and metabolic effects are generally like those of natural hormones. However, there are variations even with the same type of tumor, which suggest either departure from the natural chemical composition, alterations in metabolism of the hormone itself or changes in receptor mechanisms, or combinations of these factors. Nevertheless, the clinical picture and various methods of examination of the patient may lead to successful surgical or other forms of treatment. Most of the tumors can be identified morphologically. The endocrinologist may ultimately provide the clew to the positive diagnosis of those neoplasms of endocrine glands which still puzzle the morphologist and clinician. As is true of other fields of medicine, intelligent coöperation is the key to further progress.

RECENT ADVANCES IN THE USE OF CURARE IN CLINICAL PRACTICE*

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ON the basis of his experiments, Claude Bernard[1] concluded that curare acts upon neither nerve nor muscle but upon an entity we call today the myoneural junction. This concept is still acceptable. He then outlined future investigation in stating that it was first necessary to isolate the active chemical principle of the crude drug, after which the crucial experiment would be to determine the nature of its action, physical or chemical, on the myoneural junction.[2] The first important step was taken by King,[3] and Wintersteiner and Dutcher,[4] in isolating and identifying the pure crystalline tubocurarine. Previous to this, knowledge of the alkaloid was confused both as to exact botanical origin and pharmacologic properties. Now for the first time it was possible to evaluate a curare of known purity and predictable effect. The final step, or determination of its mode of action on the myoneural junction, is still incompletely realized.

Tubocurarine belongs to a group of compounds known as quaternary ammonium salts. In general, these salts exhibit the property of paralyzing neuromuscular conduction at the myoneural junction.[5] The majority, however, have other properties which overshadow and obscure this action. Almost alone among them, tubocurarine, in certain concentrations, has a pure myoneural junction effect.

What do we know of this property? It is most probably related to the configuration of the molecule rather than merely to chemical composition. Acetyl choline and prostigmin have similar configuration and under certain circumstances can be made to exert a curariform effect, and conversely, curare can be made to cause a muscle twitch.[6] The physical chemists have shown that molecules of this stereochemic type exert specific effects on vital membrane structure. Further study of these membrane phenomena will undoubtedly add to our knowledge of how

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the quaternary ammonium salts act. The implications of these facts are of physiological import because any data about the nature of neuromuscular conduction throws light on the entire problem of synaptic transmission in the central nervous system.

The Nature of Curare Block

Let us briefly outline one line of reasoning based on experimental facts. The myoneural junction is an excitable membrane. A transmitter substance, whether it be acetyl choline or local action currents, induces a potential by actively depolarizing the junctional region. Normally, this depolarization reaches a critical value and produces the muscle spike by spreading electronically and depolarizing the neighboring area. In fully curarised muscle, this so-called endplate potential rises to a subthreshold level and then decays without initiating a muscle response. If curare merely paralyzed skeletal muscle in this manner, it would have little clinical value in the type of cases to be discussed here. However, the size of the endplate potential depends, to some extent, on the concentration of drug.[7, 8, 9, 10, 11] Therefore, the degree of block can be controlled. Frequencies above a critical range, or abnormally sustained, can be blocked, while those of different characteristics will still evoke a normal muscle twitch. Since the normal excitatory state at the junctional membrane depends on rapid reversibility of polarization, any mechanism which either reduces this capacity or maintains the membrane in a single phase for abnormal periods of time acts as a depressant. Such a process may explain why in certain concentrations acetyl choline and prostigmin are depressants of neuromuscular conduction.

These observations underlie the present day concept of curare therapy. We do not attempt to paralyze the myoneural junction, but merely to create a block to the abnormal impulses imposed upon the myoneural junction by the disease process. It is thus perfectly feasible to obtain a therapeutic effect without loss of voluntary power.

Therapeutic Applications of Curare Action

What is the clinical value of these facts?

Review of the literature reveals that since the mid-nineteenth century curare has had sporadic clinical trials.[12, 13, 14] Because of its narrow therapeutic margin and evanescent effect, its usefulness, except in very skilled hands, has been sharply limited in spite of a sound physiological

basis.[15, 16, 17, 18]

With aqueous solutions an effective clinical response is usually associated with unpleasant side effects.[15, 16, 17, 18] Absorption is followed by high concentration and rapid elimination. At such high concentration, central and peripheral effects occur concomitantly. Prolonged duration of effect at optimal levels of concentration is thus impossible. In an attempt to avoid the toxic responses and prolong the desired effect, various vehicles were tried in this study. A suspension of d-tubocurarine chloride in white wax and oil proved best.[19] Percentage composition was based on clinical assay in an attempt to achieve adequate peripheral action without superimposed central phenomena or paralysis. The proportions in use today are 3 per cent tubocurarine in 4.8 per cent wax in peanut oil. One cubic centimeter of the suspension contains the equivalent of 175 units of standard curare.[20] The alkaloid is stable and not affected by sterilization. It is well standardized and its action predictable, milligram for milligram. The suspension is given either by the subcutaneous or intramuscular route.

The present series consists, at the time of writing, of 1500 injections ranging from 0.4 to 2.5 cc. of suspension in a group of 200 patients. Dosage requirement seems only vaguely related to body weight, but directly to disease entity. Duration of effect has been from 24 to 168 hours, and likewise related to the type of pathology. It is obvious that the effect seems prolonged over the period that curare is present in the body in perceptible concentrations. This curious fact is being investigated in the laboratory but unfortunately work is slow because no adequate method of blood level determination has been discovered.

The following types of pathology are represented in this series:

I. Muscle Spasm, as in: (a) direct trauma to muscle, (b) low back syndrome, (c) orthopedic deformities with reflex spasm, (d) myositis, (e) arthritis.

II. Spasticity, as in: (a) degenerative diseases of the central nervous system (1) multiple sclerosis, (2) disseminated sclerosis, (3) familial lateral sclerosis; (b) spinal cord injury, (c) cerebrovascular disease, (d) tumors of the brain and spinal cord.

III. Spasticity with dystonic features (Little's disease, cerebral diplegia).

IV. Dystonia and Athetosis.

V. Rigidity, as in (a) Parkinson's syndrome.

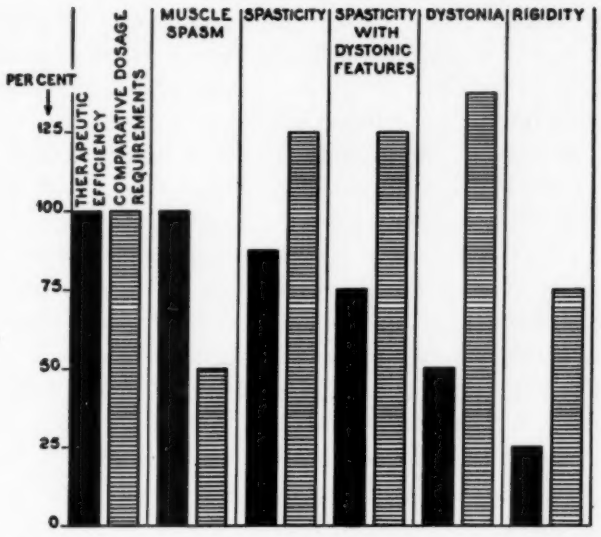

Figure 1 is an attempt to correlate statistically the comparative therapeutic efficiency and dosage requirements in the various types of pathology represented in the series. It is apparent that spasm and spasticity respond much more readily than the more complicated neuromuscular mechanisms. Dosage requirement roughly follows an inverse pattern except in rigidity. Dosage levels in rigidity differ in being a function of therapeutic response within the limits of strikingly early toxic signs and symptoms.

Therapeutic Results

I. *Muscle Spasm:* Since curare is a physiological muscle relaxant, it is not surprising that spasm responds so well. The vicious cycle of pain and muscle spasm is well known, as is the rapid relief afforded by any means which serves to break up this cycle. In this series, we have seen all degrees of spasm yield to treatment, although where the pain was based on root compression, residual root pain remained after complete reduction of reflex muscle spasm. This response is useful diagnostically in ruling out root compression as a causative factor in a clinical picture. If, after treatment, pain of radicular type persists in spite of marked diminution of spasm and diffuse pain, it is probable that root compression is the underlying cause. On the other hand, in orthopedic disturbances with reactive spasm, all the pain except focal pain or tenderness at the site of disease seems to disappear.

So many common disorders, based on the wear and tear of our mode

of life, are accompanied by muscle spasm and pain that the usefulness of a drug of specific value in such conditions needs no elaboration.

A case demonstrating the value of curare in oil in muscle spasm accompanying low back syndrome is cited:

A 48 year old male, member of a medical college faculty, over a period of years has had occasional lumbosacral pain with moderate muscle spasm. These attacks were self limited and disappeared without residue. In recent years patient has grown much heavier and has led a more sedentary existence. In February, 1946, he began to note recurrence of lumbosacral pain. This became increasingly severe over a period of days and patient was admitted to the hospital. On mild sedation, bed boards and rather haphazard traction, he improved enough in three days to be discharged. X-ray examination had revealed an unstable lumbosacral joint with proliferative arthritis in the joint region. Two days later pain had increased to its former severity and patient was again hospitalized. Muscle spasm at this time was more pronounced, and patient was in constant severe discomfort, in all positions. Traction was reinstituted without relief. Morphia and sedation were used in large doses. The orthopedic attendant advised a body spica, full length, and this was applied. The patient complained more and more bitterly, remained sleepless, and unrelieved by any form of medication. At the end of four days spinal anesthesia was contemplated in a heroic attempt to reduce the marked muscle spasm of the entire low back region with the accompanying severe pain. A trial of curare in oil was agreed upon instead. One cc. of the suspension was given in the right buttock. Two hours later the patient stated that his back muscles had relaxed and at the same time, the accompanying generalized pain had vanished. The reduction was immediately demonstrable on examination. Patient now noted only focal pain on motion at the lumbosacral articulation. Relief of pain was followed by adequate rest without medication. The patient became less tense, began to eat, and regain his normal equilibrium. However, by the third day, in dread of a recurrence, he requested a second injection. The same dose of drug was given at this time and again three days later. The spasm never recurred and the patient's subsequent convalescence was completely uneventful. A back brace was prescribed by the orthopedist and when this was fitted, the patient was allowed up, and discharged from the hospital.

II. *Spasticity:* With true spasticity it is generally possible to increase

motor efficiency by eliminating the increased excitability of the stretch reflex. Whatever the patient's motor power, it is always possible to increase its utilization by reducing the spastic element. Voluntary power is unaffected at dosage levels, sufficient to relieve spasticity. In every case in the series, gait was improved by this unmasking effect. Retraining enhanced this new level of performance strikingly. It was of interest to hear the patients repeatedly describe the degree of muscular relaxation present after the first injection. Characteristically, those with spastic lower limbs called attention to their ability to wiggle their toes or perform heel to shin tests previously impossible. This suppleness, once regained, survived in spite of termination of treatment, even though there may have been a return of considerable degree of general spasticity.

A case illustrating the effect in spasticity secondary to degenerative disease of the central nervous system is illustrated: A 38 year old male was admitted to the Neurological Institute with chief complaint of difficulty in walking. For the last 14 years he had noted increasing spasticity of the lower extremities, along with weakness, especially on the left side. One brother and a sister had the same complaints. On examination, patient walked with a marked scissors gait, with his feet crossing on forward motion. There was pronounced adductor spasm. The left leg did not flex and elevate on forward motion but instead dragged forward. There was a paucity of associated movement of the extremities. Only the toe region touched the floor during ambulation, and the heels were held three inches above the floor even with effort to walk on the entire foot. The trunk was thrown forward and there was an increase in lumbar lordosis. Clonus and increased reflexes were noted. A diagnosis of familial lateral sclerosis was made. Patient was started on 1 cc. of curare in oil twice weekly and continued on it for four weeks. Reeducation exercises in walking were given daily. Adductor spasm was rapidly reduced. Electromyograms demonstrated a drop in hyperexcitability of the stretch reflex in the lower extremities. The patient noted increased flexibility and could perform knee chest exercises and wiggle his toes freely for the first time in years. The gait rapidly changed with reduced scissors tendency and with both heels fully touching the ground in walking. In four weeks the dose was dropped to 0.6 weekly which seemed to maintain the patient at an efficient level of response. The patient was discharged in six weeks on weekly doses of 0.6 cc. administered on an out-patient basis. At the time of discharge, analysis of

moving pictures of the patient's gait revealed striking improvement. The exaggerated lordosis was gone and at rest the patient stood with legs apart and toes pointed outward. Passive stretching of the adductors did not initiate abnormal responses. In walking associated movements had rerurned, and both feet were firmly on the ground without the previous marked inversion tendency.

In *spastic paraplegia*, the use of curare in oil has proved a valuable adjunct to treatment. These cases have always been most difficult to handle, and no adequate measure has yet been described which will alleviate the distressing reflex manifestations of this condition with complete success.

In these cases it has been possible to: (1) reduce mass movements and thus aid healing of decubiti and prevent sudden expulsion of urine, (2) prevent contractures, and (3) permit active physiotherapy without acceleration of reflex spasm.

In *spastic paraparesis*, the results are even more successful. Since there is residual motor power, surgical measures designed to relieve spasticity take a toll in reducing voluntary power. It is here that curare therapy proves most valuable, by relieving crippling spasticity without sacrificing motor power.

A series of cases with an aanlysis of results has previously been reported.[20] The following case illustrates the usefulness of the drug in these cases:

A 34 year old male had suffered for 12 months from a traumatic lesion of the spinal cord at T-2 due to a gun-shot wound. A laminectomy within 48 hours after injury revealed edematous, discolored spinal cord in continuity. Within three months, there was return of crude sensation and voluntary power was noted in the left foot. Voluntary power increased regularly and within nine months patient could move all muscle groups. However, the return of motor control was accompanied by increasing spasticity in flexion. Ulceration of the mesial aspects of both knees, secondary to adductor spasm, supervened. Fibrosis and contracture at the knee joint followed the prolonged spasm. The patient complained bitterly of pain and attempted suicide in depression over the progress of events. Curare in oil was started and a dose of 1.25 cc. arrived at estimation of clinical effect. The patient began to note relaxation of spasm at 45 minutes and maintained it for an average of 72 hours. His subjective symptoms disappeared at the same

time. He was encouraged to move about freely and to exercise actively. He noted no increase in paresis during his periods of relief from spasticity. Physiotherapy was started and vigorously pursued during these periods. The ulcerations of the knee region healed spontaneously as adductor spasm was dissipated. Muscle tone and volume improved. Over a period of 2 months, there was a perceptible decrease in spasticity over and above drug effect. In spasticity, duration of beneficial effect is usually of long duration and in general, patients do not return to their original level of dysfunction when therapy is discontinued.

III. *Birth injuries, cerebral diplegia or spasticity with dystonic features:*

In his monograph on disorders of the central nervous system in children,[21] Crothers states: ". . . it is essential to develop every motor asset in sight. This conservation and development of assets is procured by two different but closely coordinated methods: first and always, by training, and second, by procedures which avoid or correct contractures." Achievement of both these objectives is facilitated by the use of curare in oil. Training capacity is markedly enhanced by the reduction of abnormal activity, with a consequent increase in motor efficiency. The same reduction in spasticity or abnormal muscle tensions also allows a range of motion and activity which prevents further fixation deformity or contracture. Unlike surgical procedures designed to this end, it is unnecessary to destroy innervation or reduce the number of functioning motor elements contributing to the deformity. Effective diminution in abnormal motor activity can be obtained without perceptible loss of motor power.

One has only to watch these children at school to realize the titanic effort which goes into every attempt at motor performance. In light of this, the degree of their achievement under this form of therapy might seem slight to the casual observer. Nevertheless, by objective performance standards the improvement in motor performance is striking. The same tremendous drive which characterizes their usual effort now pushes their performance levels forward at rapid rates.

Improvement can be expected in the following sequence: (1) speech, (2) ability to sit quietly, (3) gait, and (4) eating, writing, and performance of all skilled motor activities. These patients have maintained their improvement on doses twice weekly.

IV. *Dystonia and Athetosis:* It has been possible here to: (1) Re-

duce spontaneous movements so that patients can sit quietly for reasonable periods, (2) make active exercise and motor training possible, often for the first time, and (3) improve sleep.

V. *Rigidity as in Parkinson's Disease:*

Efficacy of treatment in these cases is most difficult to evaluate. It can be definitely stated that rigidity is an indication, tremor not. Rigidity associated with extreme discomfort, immobility and beginning contracture can be partially alleviated. Sleep is invariably improved, which means much to Parkinsonians. Pain associated with long standing muscle tension can be influenced to a gratifying degree. In rigidity there is, however, a wide disparity in response, and in dosage tolerated.

It is not surprising that there should be such a wide variance between the effects in spasticity and in rigidity. Spasticity depends upon a hyperexcitability of reflex mechanisms such as the stretch reflex, whereas rigidity is a function of simultaneous innervation of agonists and antagonists in addition to reflex mechanisms.

General Observations: Patients almost invariably note a pleasurable feeling of relaxation within two hours after injection. Under favorable conditions, in fact, most of them doze during this period. There is an associated fall in systolic pressure, averaging 20 points, which is related to muscle relaxation, and not a specific vascular effect.

Recognizing the general sedative effect, a series of cases showing motor acceleration on a psychiatric basis has been treated. The early results are very interesting, but unfortunately, inconclusive at this time.

We have seen no side effects of clinical significance in what we consider our therapeutic range. Once concentrations pass a critical level, however, central effects supervene with mental confusion and a feeling of marked tenseness in addition to the classical toxic signs.

There have been no toxic effects on any organ system over periods of time, and no changes in body economy or general well being. No tendency to habituation has appeared in this series, although one patient has had more than 75 injections. Contraindications specifically are: (1) any myasthenic tendency and (2) kidney disease. Since curare is eliminated largely unchanged in the urine, poor renal function conceivably could elevate blood concentrations to a dangerous degree.

In summary, an improved vehicle along with a well standardized drug has permitted us to exploit the physiological properties of curare. In a series of 1500 injections in various syndromes, no alarming toxic

reactions have occurred. The major number of patients have been ambulatory and at their normal occupations during treatment. In therapeutic dosage range the drug has been singularly free of side effects, and has shown no tendency to disturb the normal body economy or cause habituation. Statistically, spasm, spasticity, and rigidity are affected in order of decreasing efficiency. Dosage levels are strikingly related to the degree of motor acceleration. Duration of effect also seems inversely proportionate to the degree of motor spontaneous activity.

On the basis of this, and further studies, it is hoped that the usefulness and safety of this tool may be increased, particularly since its field of action is one characterized by disease entities which are singularly refractory to treatment.

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SUMMARY OF THE PRESENT STATUS OF OUR KNOWLEDGE OF THE FACTORS CONTROLLING BLOOD PRESSURE*

GEORGE A. WOLF, JR.

THE sequence of events which presumably occur when the blood pressure rises is illustrated in Figure 1. In brief a stimulus may activate receptors, impulses from which arrive in the integrative areas of the central nervous system and presumably are distributed via humoral and nervous means to the peripheral vessels. There vasoconstriction and increased peripheral resistance result in elevation of the blood pressure. Other factors which are known to increase blood pressure are included in the diagram.

It is proposed to discuss the events in this "reaction chain" in terms of the role they play in increasing the blood pressure. Environmental stimuli which are known to cause brief elevations of the blood pressure are cold, inhalation of irritant gases, pain, muscular activity[1] and stress producing life situations associated with emotions. Most recently attention has been focussed upon the latter group of stimuli. It has been observed that situations which give rise to anger, aggression, rage, resentment, and frustration are frequently associated with elevations of the blood pressure and an over response of the blood pressure to exercise.[2] These reactions may be sustained. Furthermore, many patients with hypertension have been found to have personalities distinctive in that they are easily aroused to anger and resentment. Such patients restrain their feelings but are subject to temper outbursts.[3, 4] Increased cardiac output and increased peripheral resistance play a role in the genesis of this type of hypertension.[2]

There is no evidence that receptor organs are concerned with the regulation of blood pressure other than the fact that they receive stimuli from the external environment.

Integrative function refers to that function of the central nervous

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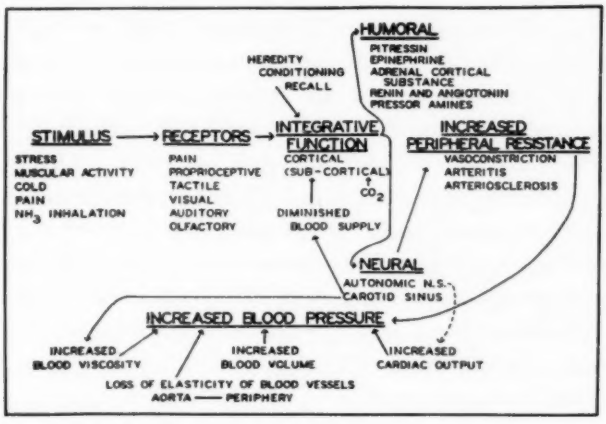

FIGURE I

system which concerns itself with the modification of impulses resulting from environmental stimuli. Interpreted more broadly it may refer to that mechanism which governs the quality and quantity of the reaction of an organism to a given stimulus. Relevant to the problem of blood pressure control it can only be said that conditioning and heredity may exert their influence on this function. Some data are available, however, on the subcortical mechanisms which control blood pressure. Reduction in the blood flow[5] to the vasomotor "centers" and increase in the carbon dioxide content[6] of the blood supplying these areas may give a pressor response. Anatomic evidence of impaired blood supply to vasomotor centers cannot be found in patients with hypertension.[7] It is probable that these areas can be activated by impulses arising in the cortex and influenced by pressor substances in the blood. In addition it is possible that impulses mediated through this area may activate humoral as well as neural mechanisms.

Renin produced by altering the renal blood flow when incubated with hypertensinogen produces hypertensin (angiotonin) which is a pressor substance. Small amounts of renin have been detected in the renal vein after temporary arrest of the renal blood flow in humans.[8] However, attempts to detect renin and hypertensin in the blood of patients with essential hypertension have met with failure.[9] In the blood of patients with glomerulonephritis and malignant hypertension renin,

angiotonin and protein vasoconstrictor substance have been detected.[9, 10] There is no definite evidence that anatomical impairment of the blood supply of the kidney is present in essential hypertension, and indeed study of the renal blood flow by indirect methods does not reveal functional impairment of the renal blood flow in essential hypertension in the initial phases of the disease.[10] It is not clear, however, that an absolute reduction in the renal blood flow is necessary to the production of renin in animals as it can be produced by lowering the pulse pressure in the renal arteries.[7] Hypertensin acts directly upon the blood vessels causing vasoconstriction,[11] and its pressor activity may manifest itself in animals with neurogenic hypertension effected by section of the moderator nerves.[12] It is further possible that neural processes may initiate vascular changes leading to the production of renin.

Pressor amines have been found in the ischemic kidney[13] and the *in vitro* study of these substances has revealed that deaminization occurring in the presence of oxygen has resulted in a loss of the pressor properties. Although substances such as these may be active in the control of blood pressure their pressor effect includes an increase in cardiac output and a diminution in the peripheral blood flow not found in essential hypertension.[14] That these substances are relevant to the control of human blood pressure has not been shown.

Pitressin and epinephrine produce vasoconstriction directly. This occurs in the peripheral vessels reducing the peripheral blood flow and in addition may affect the renal blood flow. Evidence that hypersecretion of the pituitary and adrenal medulla occurs in essential hypertension has never been found and the vascular changes produced do not resemble those found in essential hypertension.[10] On the other hand, patients with hypertension who developed Addison's disease have been shown to have a recurrence of their hypertension when substitution therapy with desoxycorticosterone was provided.[15] Adrenal ischemia will produce hypertension in dogs.[16]

The recent detection of a substance (VDM) in shock in animals has led to the postulation of a normal balance between vasoconstrictor substances and vasodilator substances. It is suggested that alteration in this balance by overproduction of vasoconstrictor substances or diminished formation of vasodilator substances may result in the hypertensive state. The vasodilator substances were found in greatest concentration in the liver of the shocked animals.[17]

Impulses mediated through the sympathetic nervous system result in vasoconstriction. This may occur in the splanchnic bed, peripheral arterioles and in the renal arterioles. Thoraco-lumbar sympathectomy does not increase the renal blood flow but it may result in a fall of blood pressure.[11] Section of the moderator nerve to the carotid sinus results in a persistent hypertension (4 years in animals),[18] and in one instance bilateral section of the glossopharyngeal nerves in man resulted in a sustained hypertension (4 weeks).[19] The problem exists as to what part the splanchnic circulation as contrasted to the peripheral circulation plays in hypertension.

There seems to be little doubt that elevation of the blood pressure in hypertension is caused by increase in the total peripheral resistance of the arteriolar bed, which in the early stages is functional and not anatomical in nature. It has been suggested that changes in the distensibility of the great arteries alter the cardiodynamics.[11] It is probable that the sensitivity of the arterioles in hypertension is not increased to ordinary pressor stimuli. An arteriolitis can cause an elevation in blood pressure but it is probable that such changes do not occur early in hypertensive disease.

Other changes which serve to increase the blood pressure but which do not seem to be relevant to the problem of essential hypertension include: increased blood viscosity, increased blood volume, loss of elasticity of the vessels, and increased cardiac output.

In considering the problem of hypertension in relation to those mechanisms which control blood pressure, one is impressed with the idea that early essential hypertension is a functional state. Indeed the notion of balance or interaction between the various mechanisms of blood pressure control and the notion of reaction of the total organism to his environment are attractive. Such statements are speculation and that unknown mechanisms of blood pressure control are present is quite possible. However, it is becoming increasingly doubtful that a single defect in those factors controlling blood pressure is the cause of hypertension.

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APICAL SYSTOLIC MURMURS IN INCIPIENT RHEUMATIC HEART DISEASE*

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An apical systolic murmur, as the initial and sole sign of early rheumatic heart disease, deserves wider recognition than it has usually been accorded. This discussion will be confined to the diagnostic significance of apical systolic murmurs in cases of incipient or dormant rheumatic heart disease, in which the signs of advanced valvular disease—heart failure, enlargement of the heart, diastolic murmurs, and abnormal electrocardiograms—are not present to confirm the diagnosis.

Wartime conditions afforded an unprecedented opportunity to observe cases of incipient heart disease which under ordinary circumstances would not come to a physician's attention. Lessons learned from experience in the armed forces are equally applicable in civilian life where persons with incipient or dormant heart disease will likewise develop disability when overtaxed by heavy physical work or undue mental or emotional stress.

The significance of the loudness or intensity of the systolic murmur is to be evaluated, not its transmission, since the latter depends solely on the loudness of the murmur.[1]

The importance of the problem is emphasized by the incidence of apical systolic murmurs. Fahr[2] states that it has been estimated that of all children from 6 to 14 years of age, 40 to 70 per cent present apical systolic murmurs; in the second decade of life, 35 per cent of all normal persons manifest it; in the third decade, 22 per cent; in the fourth decade, 19 per cent.

In the literature there are to be found two opposing views on the significance of systolic murmurs unaccompanied by other symptoms. The older one, prominent before World War I, assumed that all sys-

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tolic murmurs were serious, that young women who presented this condition must never marry, let alone bear children. A patient with a systolic murmur was given a lugubrious prognosis. The opposite opinion was shared by Mackenzie,[3] Cabot,[4] and more recently by Blumenthal.[5] These authors attached no importance to a systolic murmur, even when a patient reported a history of rheumatic fever, provided the heart was not enlarged, diastolic murmurs were not audible, heart failure had not occurred, and electrocardiographic abnormalities were not present.

As so often happens in wide divergences of opinion, the truth lies between the two extremes. Scott,[6] Levine,[7] and Sodeman[8] believe that any murmur is significant, and that the importance of a murmur increases as its loudness is intensified. It is my belief that a moderately loud or loud systolic murmur certainly should be considered to be organic in nature until it is proved otherwise.[9] Shapiro[10] is in accord with this interpretation. In other words, if a loud systolic murmur is audible at the apex, the presence of valvular heart disease cannot be ruled out on the basis that heart failure, enlargement of the heart, history of rheumatic fever, or abnormal electrocardiogram are not also present.

Freeman and Levine[11] classified systolic murmurs into six grades of loudness. In this discussion I have accepted their contention that adventitious sounds of intensity of grade III and louder are organic in nature: that is, the moderately loud, the loud, or the very loud systolic murmur at the apex is a physical sign of serious importance. This does not mean, of course, that a person with this type of murmur should be considered as an invalid. On the contrary, the vast majority can carry on all normal activities, except that they should not be exposed to extremes of physical or mental exertion.

Insurance statistics[12-19] prove beyond doubt that apical systolic murmurs, even in the absence of other signs of organic heart disease, are indicative of organic heart disease. Individuals so affected are subject to a heightened mortality rate. Bonnett[12] reported that among insured persons with this sole apical murmur, the mortality rate for those performing light work was 218 per cent, and for those doing heavy work, 293 per cent. For those under forty years of age, the figure became 325 per cent, and if there was a history of rheumatic fever, the rate increased to 453 per cent. The normal expected mortality rate was taken as 100 per cent. Hunter[14] also found that among manual workers with this type of murmur, the mortality rate was 50 per cent higher than it was

among white collar workers.

Not only an increased mortality rate, but also certain clinical implications are to be noted in cases of this type. Thirty to 50 per cent of patients with rheumatic fever develop disease of the mitral valve, and 20 to 25 per cent of these become victims of subacute bacterial endocarditis. Valvular disease is often overlooked during life and found only at death or when subacute bacterial endocarditis is discovered.

Certain difficulties are inherent in the evaluation of systolic murmurs. In the first place, systolic murmurs exhibit variations. They may be loud in one examination and not audible in the next. They may vary with changes in position of the patient. They may disappear for weeks, months, or years, and then reappear. Coombs[20] stated that 31 per cent of the signs of rheumatic fever may disappear. In a follow-up of 1000 patients with valvular heart disease, Bland, Jones, and White[21] discovered that physical signs regressed in a considerable number, and that in 83 instances (8.3 per cent) there was a total disappearance of all physical signs. May Wilson[22] reported similar observations. I have seen a patient with rheumatic fever, pericarditis with large pericardial effusion, definite mitral and aortic disease, and enlarged heart, who was completely free of physical signs at the end of three years. Swift[23] is of the opinion that rheumatic valvulitis may clear up entirely, in much the same fashion as does the swollen ankle in rheumatic fever. Wilson[22] believes that minimal scarring of the valves always remains.

Another difficulty in the evaluation of apical systolic murmurs arises from the fact that both a patient and his family may have forgotten that he has had rheumatic fever. Scott[6] and Hedley[24] pointed this out. In the initial examination of men drafted for the Army, Flaxman[25] found that 52 per cent (more than half) of those who exhibited systolic murmurs of organic nature gave no history of rheumatic fever. Levy, Stroud, and White[26] reported that of the men from four cities rejected for military service, only 28.8 per cent of those with organic valvular disease gave histories of rheumatic fever.

Finally, there is the difficulty presented by differential diagnosis. This will be discussed in detail later, but it is well to mention here that apical systolic murmurs of organic origin must be differentiated from the loud murmurs that are heard in neurocirculatory asthenia and in cases of chest deformities, especially those produced by a flat or funnel-shaped thorax. A systolic murmur is frequently simulated by a split

first sound or by a systolic gallop; in fact, the latter may give the impression of a presystolic murmur.

In earlier reports[9, 27, 28] I cited instances among naval personnel which affirm the need for accurately evaluating apical systolic murmurs. Early valvular disease was first revealed when these men were stationed in the South Pacific area during 1942. They developed the signs and symptoms of heart failure; they complained of pain, fatigue, and shortness of breath. Their past histories recorded questionable heart murmurs heard by their family physicians, insurance doctors, or the recruiting officers at the time of enlistment, but the murmurs had not been regarded as significant. Other instances of unsuspected early heart disease were found in the course of reëxamining men whose health records had been lost in the sinking of ships. More than half of the men gave past histories of rheumatic fever, and many of them experienced recurrences of the disease.

Diagnosis

Bearing in mind the factors which tend to complicate the diagnosis of apical systolic murmurs, careful examination of the patients should make it possible to establish the nature of a murmur.

History. As already pointed out, loud apical systolic murmurs occurring in patients who have a history of rheumatic fever is almost certain evidence that disease of the mitral valve exists. Equally significant is a history of an infection by the group "A" Streptococcus hemolyticus, since rheumatic heart disease may be associated with infections of this type. In a recent report, Watson, Rothbard, and Swift[29] demonstrated the relationship of scarlet fever to rheumatic fever and rheumatic heart disease, on the basis of this streptococcus.

Physical examination. In the type of heart disease under discussion, enlargement of the heart is not observed, an apex thrill is not felt, nor is a diastolic murmur routinely audible. The first sound at the apex is loud, as is the second pulmonic sound. The murmur at the apex is loud and prolonged; it begins and is concurrent with the first sound. The presence of a "musical" murmur, a "sea gull" murmur, a "harsh" murmur, or a "constant" murmur, is of additional diagnostic value. If a loud, long murmur has been once heard or reported, or if for any reason there is suspicion of organic heart disease, the patient should be examined again and again in all positions. Hope,[30] as early as 1832, described the

evanescent character of mitral murmurs. The left lateral recumbent position and the sitting position with the patient leaning forward and to the left are the most advantageous. Auscultation after exercise or after inhalation of amyl nitrite is helpful. These maneuvers may elicit not only a loud apical systolic murmur which will persist for some time, but they may also disclose the presence of a diastolic murmur, thereby confirming the diagnosis of mitral valvular disease.

Phonocardiogram. The phonocardiogram has been found to be a useful diagnostic aid. It may prove that the murmur is prolonged throughout the systole (holosystolic), and it may also disclose an inaudible diastolic murmur.

Teleroentgenogram and fluoroscopy. In early or incipient (or occult) valvular disease, neither teleroentgenographic nor fluoroscopic study will reveal enlargement of the heart, appearance of the left auricle far over on the right side, and indentation of a barium-filled esophagus. However, these examinations frequently disclose straightening of the left border of the heart; that is, prominence in the region of the pulmonary artery and left auricular appendage. A characteristic sign may be obtained by examining the patient in the left oblique position. It will be seen that the left auricle has begun to enlarge, and that it fills the space under the left main bronchus but does not elevate it. Elevation of the bronchus occurs only with advanced left auricular enlargement.[9, 31]

Electrocardiogram. The electrocardiogram is not of much value in the diagnosis of early mitral disease. However, deformity of the mitral valve may be suspected if there is present right axis deviation of the QRS, a P-wave more than 2½ mm. in amplitude, a P-wave at least 0.10 second in duration, or a well-notched P-wave.[31, 32, 33]

Differential Diagnosis. Neurocirculatory asthenia or effort syndrome or "small" heart syndrome and certain deformities of the chest are conditions which most frequently offer problems in differential diagnosis. In the former condition, a systolic thrill may be felt, and a loud apical systolic murmur may be heard concomitantly with a loud first sound at the apex and a loud second pulmonic sound. To add to the difficulty but also to the interest of the problem, the x-ray film will demonstrate a straight left border of the heart and the electrocardiogram may disclose the abnormalities previously described for mitral valvular disease.[9, 31, 34] However, keeping in mind that a patient with effort syn-

drome exhibits signs that are also present in mitral valve disease, the differentiation can usually be made on the basis of recognized symptoms of neurocirculatory asthenia. Furthermore, a patient with effort syndrome is thin, possesses a low diaphragm with a long, narrow or small heart; he is nervous, has a tremor, complains of dizziness and giddiness, often of severe precordial pain unrelated to effort, and presents symptoms of anxiety neurosis.

Discussion

Incipient valvular heart disease manifested only by a loud apical systolic murmur is observed more frequently among men in the armed forces than is advanced disease of the mitral valve. This apparently higher incidence during wartime is attributable, of course, to the fact that persons with pronounced signs of mitral valvular disease are not accepted into the armed forces, whereas in civilian life the physician usually sees those patients who seek advice because of the severity of their symptoms. Actual battle conditions will cause the breakdown of a man with early or dormant valvular heart disease who might, in civilian life, live for years—in fact, to old age—without knowledge of his heart defect unless he worked at heavy manual labor or was subjected to unusual emotional strain or entered competitive sports such as football and tennis. In many instances, rheumatic heart disease is discovered only at autopsy or when the patient first develops subacute bacterial endocarditis in middle or in old age.[35] In a study of 100 consecutive autopsies on patients who died of acute coronary artery occlusion,[36] 17 patients were found with definite rheumatic valvular disease, only 8 of whom had had symptoms or knowledge of the disease during life.

Although a history of rheumatic fever or evidence of infection by the group "A" Streptococcus hemolyticus is of utmost value as evidence for the organic nature of a loud apical systolic murmur, it should be recalled that 20 to 25 per cent, and perhaps even as many as 50 per cent, of the patients do not give a history of rheumatic fever.

In the evaluation of apical systolic murmurs, the loudness or the intensity of the murmur is of more significance than its transmission. As Levine and Likoff[1] have shown, the louder the murmur, the greater the transmission. In doubtful cases, a phonocardiogram will establish the length of duration of a murmur and will also reveal the presence of any murmur which may not be audible. At the present time, a good portable

stethographic machine is on the market.

To be of value as evidence of organic heart disease, it is not enough that exercise produce a systolic murmur at the apex. The murmur must be loud, prolonged, and of some duration. In other words, the loud murmur must persist for a longer period than is to be expected from the effect of exercise alone. Effort, particularly if strenuous, produces murmurs in a healthy person, but these will disappear almost immediately with cessation of the exertion and certainly with the slowing of the heart.

The necessity for repeated examination of all patients in whom there is a question of the significance of a systolic murmur cannot be emphasized too strongly. Examination time and again, in different positions and following exercise, will often be required, because in early cases of valvular heart disease, the murmurs are transient.

One of the most useful indications of beginning mitral valvular disease is to be found by teleroentgenographic and fluoroscopic examinations. The left auricle enlarges to the left and upward before it enlarges posteriorly and to the right, thus producing the prominence in the region of the pulmonary artery and left auricular appendage. The left main bronchus is not yet elevated, nor is the barium-filled esophagus indented, but in the left oblique position the left auricle fills the lung space under the left main bronchus. Grishman, Sussman, and Steinberg[37] believe that the prominence in the region of the pulmonary artery is caused by the pushing up and to the left of this vessel by the enlarging left auricle.

The electrocardiogram, useful in advanced or moderately advanced mitral valve disease, is only occasionally of aid in the type of incipient heart disease under discussion.

Cabot[4] has often been quoted by those who believe that an apical systolic murmur, whatever its character, is not indicative of heart disease unless it is accompanied by other signs of cardiac disease, such as enlargement of the heart, presence of a (diastolic) murmur, or evidence of heart failure. It is my belief that this view proves only that pure mitral insufficiency is rare. A systolic murmur alone is important to the recognition of the early mitral valvular defect—enlargement and diastolic murmurs come later. It is probable, however, that even in early cases, postmortem examination would undoubtedly reveal some anatomical evidence of stenosis.

Although the purpose of this paper has been to prove that a loud apical systolic murmur should be accepted as evidence of organic mitral valvular disease even in the absence of other physical signs, it is not my intention to imply that a patient with this sign should be treated as an invalid. Even in wartime he may be assigned to limited duty without untoward effect, and in civilian life he can carry on practically as well as a normal person, barring undue physical or mental exertion.

Summary

1. The loud apical systolic murmur unaccompanied by any other sign of valvular heart disease has been discussed. The murmur is evidence of incipient or latent heart disease.

2. Patients with beginning valvular heart disease break down in wartime and also under peacetime conditions if they are exposed to severe or continuous physical exertion or emotional stress.

3. The war presented an unusual opportunity to see cases of this early heart disease, but the lessons learned are applicable to civilian practice.

4. Insurance figures reveal an increased mortality rate among persons whose only sign of heart disease is a loud apical systolic murmur.

5. Certain difficulties are encountered in evaluating apical systolic murmurs; i.e., murmurs vary; they appear and disappear and apparently often regress completely; a history of rheumatic fever may not be obtained in half the cases of organic valvular disease; the problem of differential diagnosis is ever present. The very appreciation of these difficulties facilitates interpretation of the murmur.

6. A history of rheumatic fever or of any disease attributable to the Group "A" Streptococcus hemolyticus is corroborative evidence of heart disease.

7. A careful physical examination may uncover physical qualities of the murmur in addition to its loudness, which add to its significance. A loud first sound at the apex, a loud second pulmonic sound, a holosystolic murmur, a "musical" murmur, a "harsh" murmur, a "sea gull" murmur, a "constant" murmur, all lend importance.

8. Repeated examination, in many positions, and after exercise may be necessary. Furthermore, a diastolic murmur may be discovered.

9. Exercise is useful only if a loud or a prolonged systolic murmur results and persists for a longer period than is to be expected from the

effect of the exertion alone. The murmur must remain at least until the heart rate slows.

10. The phonocardiogram is valuable in proving the presence and the duration of the systolic murmur and in demonstrating an unsuspected diastolic murmur.

11. The x-ray film and fluoroscopic examination help in revealing a straightened left border of the heart and, more particularly, filling in by the left auricle of the space under the left main bronchus. This is an early sign of left auricular enlargement and appears long before the esophagus becomes indented or the left auricle moves to the right side of the heart.

12. In the presence of heart failure, there may be no obvious enlargement of the heart in beginning valvular disease.

13. The electrocardiogram is only occasionally of service in early valvular heart disease.

14. In differential diagnosis, the important conditions to bear constantly in mind are (1) effort syndrome or neurocirculatory asthenia (the "small" heart syndrome), (2) the funnel-shaped and the flat chest, and (3) a split first sound. One must also think of hypertension, hyperthyroidism, and anemia in the differential diagnosis.

15. The loudness or intensity of a murmur is more significant than the transmission. The latter depends on the former.

16. Incipient valvular heart disease occurs as frequently in peacetime as in wartime, but under the latter conditions a patient is likely to break down, whereas in civilian life he may live with unsuspected heart disease to a ripe old age. In fact, heart disease may be discovered only at post-mortem examination or when subacute bacterial endocarditis develops. The man or woman in ordinary life will carry on a normal existence provided he or she does not attempt heavy physical labor or work under undue emotional strain. Although loud apical systolic murmurs in early heart disease always have a practical importance, even in wartime the patient may be fit for limited duty.

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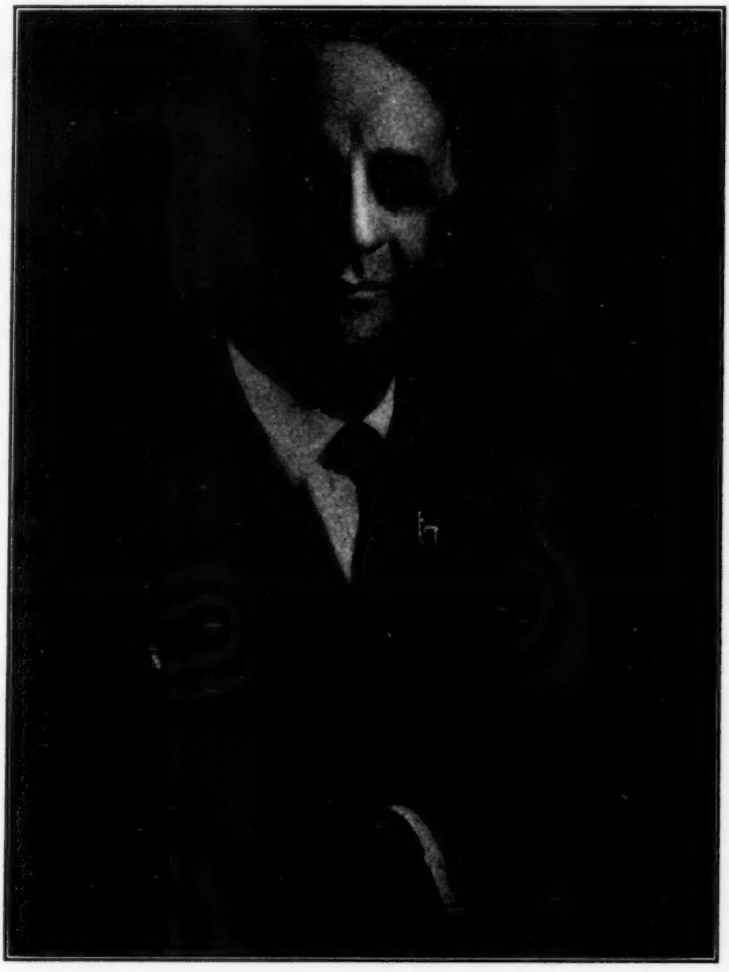

SIMON FLEXNER

1863 - 1946

IN MEMORIAM

SIMON FLEXNER

DR. SIMON FLEXNER, Member Emeritus of the Rockefeller Institute for Medical Research, died May 2, 1946. A distinguished and able scientist, he played a very important rôle in the advancement of medical science in this country. Living during what he has called "The Heroic Age of American Medicine," he was one of the leading figures in the period during which medicine in this country advanced from a very inferior position, as regards science, education and practice, to the commanding place it now occupies.

He was born in Louisville, Kentucky, March 25, 1863, and received his preliminary education in the public schools of that city. His father was a druggist, and Simon, after leaving school, became a clerk in his father's store. His mother and father were ambitious for their children, and had high ideals and a great respect for education and learning. They must have had great native ability and were suitably mated, for all their sons later rose to positions of distinction and importance. Simon early showed an enterprising spirit and an interest in what was occurring in the medical world, for even while working in the drug store, he was making sputum examinations for the Louisville doctors, and this only a few years after the tubercle bacillus had been discovered.

After several years in the drug store, he entered the Medical School of the University of Louisville, from which he graduated in 1889, with the degree of M. D. Even in those days of incompetent medical schools in this country, this school was of relatively inferior rank, and it is remarkable that with this scanty and deficient formal education, he could later have become a learned and cultivated man and a leader in the science of medicine.

His education really only commenced when he decided to go to Baltimore to study pathology under Dr. William Welch, who, a few years previously, had been appointed Professor of Pathology in the Johns Hopkins University, and who, at this time, was teaching post-

graduate students in the Johns Hopkins Hospital. At Johns Hopkins, Flexner breathed a new, rare and stimulating atmosphere. During the previous half century, leadership in pathology and medicine had passed to Germany. Great advances in physiology were being made by the pupils of Johannes Müller and especially by Ludwig, and the study of pathology was being actively prosecuted by Virchow, Rokitansky, Cohnheim and their students. Moreover, the recent advances in bacteriology were opening up wide vistas in knowledge concerning the etiology of the infectious diseases. Notwithstanding the brilliant experimental investigations of Claude Bernard and the discoveries of Pasteur, the most gifted young American students of medicine were being attracted to Germany rather than to France. This was probably due, not only to the ability of the teachers in Germany, but also to the development of the German universities, especially in science, and the stress that was being laid in them on experimental research. Young American students, like Welch and Prudden, came back from Germany bringing with them knowledge of the new techniques in bacteriology and, more important, filled with enthusiasm for promoting further advances on this side of the water. Johns Hopkins, with its relatively large endowment and the high idealism of its founders and promoters, seemed the place of greatest opportunity. As a result, there collected about Welch and the other young professors a group of gifted young men eager to carry on research. None of them responded more readily to the stimulating atmosphere than did Flexner. He had been there but a short time when independently, and unknown to Welch, he carried out an investigation, the results of which were considered worthy of publication. Welch soon recognized Flexner's ability, and when Flexner consulted him about taking his course in bacteriology, Welch replied, "There is no occasion to enter the course; study a problem." During the remainder of his life, Flexner learned by studying problems, and he never was without one. Moreover, he seemed to choose his problems with unerring skill, always selecting them in fields promising a rich harvest, and avoiding working in fields which at the time were unsuited for cultivation.

He was soon (in 1891) appointed a Fellow in Pathology, and he continued to be associated with the Johns Hopkins University and Medical School until 1899. In 1893 the Medical School was opened, and thenceforward he was engaged in teaching as well as research, and he

proved to be a stimulating and capable teacher. During his last year he had the title of Professor of Pathology. This year he was made a member of a commission sent by the University to the Philippine Islands to study the diseases prevailing there. He made a thorough investigation of dysentery, and succeeded in isolating a bacillus which he demonstrated to be the etiologic agent in many of the cases. This organism has since been known as the Flexner bacillus. On his return, he accepted an appointment as Professor of Pathology at the University of Pennsylvania.

But at this time other events were occurring which were to change the course of his career, and also to influence profoundly the course of scientific medicine. Mr. Frederick T. Gates, a layman and an advisor to John D. Rockefeller, became interested in medicine and was impressed by the great poverty of accurate knowledge concerning disease. He decided, "that medicine could hardly hope to become a science until it should be endowed, and qualified men be enabled to give themselves to uninterrupted study and investigation." He persuaded Mr. Rockefeller to make a gift for this purpose, and he consulted Dr. Welch and others in regard to the appointment of a man to head this undertaking. The position was offered to Dr. Flexner. The funds available at first were very moderate and the future seemed uncertain. But Flexner's imagination was aroused and he decided to undertake the new adventure, even at what seemed to be a personal sacrifice.

The first laboratories of the Rockefeller Institute for Medical Research were opened in 1904, and from that time until his death, Dr. Flexner was associated with this institution. He acted as Director until his retirement in 1935, after which the title of Director Emeritus was bestowed upon him. From the beginning, he made it clear that he had no desire to convert the Institute into a Flexner Institute. A few years previously other institutes for medical research had been established in Europe, notably, the Pasteur Institute in Paris and the Institute for Infectious Diseases in Berlin, the latter soon being known as the Koch Institute. Flexner's conception of an institute for medical research was much broader than that of an organization developing around the work of an individual, however great a genius that individual might be. In addition to the laboratories of pathology and bacteriology, where Dr. Flexner's immediate interests were centered, there were laboratories of physiology and pharmacology and of biological chemistry. He saw

that advances in medicine are dependent on advances in the underlying and fundamental sciences. However, in view of Dr. Flexner's training, and because of the great interest at the time in pathology, and especially in bacteriology, it is understandable that the first important problem undertaken should concern one of the infectious diseases. At this time an epidemic of cerebro-spinal meningitis was prevailing in New York City, and Dr. Flexner and his associates immediately began an investigation of this disease. They succeeded in developing an immune serum, and devised methods for its therapeutic use, that had great value, and has been efficacious in saving many human lives. At the same time, other important contributions were being made in the various laboratories of the Institute.

A few years later, another epidemic occurred in New York, this time due to infantile paralysis. Again Dr. Flexner and his associates undertook a very extensive investigation in order to learn the nature of the malady. Among many other important contributions that were made, Dr. Flexner showed that the disease could be reproduced in monkeys by the inoculation of material from a fatal human case after this material had been passed through a filter which would remove all bacteria. He thus demonstrated that the infectious agent in this disease is a so-called filterable virus. Later Dr. Flexner added much to knowledge concerning other infectious diseases, especially to knowledge concerning sleeping sickness (lethargic encephalitis). He was an able and productive investigator.

But, important as his own scientific discoveries have been, his most important contribution has been the development of the Rockefeller Institute and the influence which he and it have exerted on the advancement of experimental and scientific medicine. Under his direction, the Institute has grown from its very modest beginnings to its present size, with its large resources and large staff of investigators working in a great variety of fields. Vastly more significant than its growth in size, however, is the fact that he has endowed it with the highest ideals of scientific work. Under his direction, the Institute has concerned itself with problems of a fundamental character, and has avoided undertaking studies of a transient and superficial and trifling nature. In order to make the Institute as productive as possible, it was necessary to recognize and support ability and genius wherever found, and in whatever garb. It was also very important to make sure that they were not merely

impudence and folly in disguise. To do these things requires even more skill than to make scientific discoveries. Time has shown that Dr. Flexner was an expert impressario and that he made few mistakes. It was important that the workers be given the greatest freedom, but they had to be guided and protected, even against themselves. While never a dictator, Dr. Flexner was always the director. On one occasion, it was suggested by one of the workers, whose previous experience had been in academic life, with frequent committee meetings and formal conferences, that the members of the staff should take a more important part in the management, and a meeting was held for organization. At the meeting, it was unanimously agreed that no one except Dr. Flexner was capable of heading the organization, and he was elected president. The president never called another meeting, and the organization was never heard of again. Dr. Flexner always consulted with his associates informally before making important appointments or deciding changes in policy, but he felt that scientific investigators should be relieved so far as possible from the details of administration. The wider significance of the development of the Rockefeller Institute is shown by the establishment and growth of many other research institutes, both here and abroad, institutes not only for the study of disease, but research institutes covering many fields of human endeavor, even industry and commerce. Some of them have been directly patterned after the example of the Rockefeller Institute; all of them have been greatly influenced by the ideas and ideals of Dr. Flexner.

Less direct, though of very great importance, is the rôle which he has played in the improvement in medical education which has occurred during the period of his scientific life, and in which his brother Abraham has taken so important a part. Simon did not have the qualities of a reformer, or an advocate, or a pleader. His influence has been exerted largely through example. But it is evident that without teachers who were trained in scientific methods, and were imbued with the enthusiasm which is inspired by scientific progress, education, no matter how large the material resources, could not advance very far. In transforming the teachers in the medical schools from mere retailers of knowledge into true scientists, Dr. Simon Flexner has had great influence. As a very influential member of the Rockefeller Foundation, which has contributed so lavishly to the endowment of medical education in this and other countries, he was able to be of very great help in charting the

course along which the advances have taken place. As a member of the Board of Trustees of Johns Hopkins University, he had a direct influence on the conduct of that Medical School.

He has also influenced the practice of medicine, not merely by increasing and improving the armamentarium of the physicians by increasing their available knowledge and supplying new methods, but he has helped to make them accurate, scientific workers. In 1909, a hospital was added to the Institute in order that disease as it occurs under natural conditions could be observed and studied. Largely due to the influence of Dr. Flexner, it was provided that the physicians in the hospital should not only have charge of the treatment of the patients, and observe the superficial characters of disease, but that they themselves should at the same time be actively engaged in investigating the underlying phenomena. Besides making important contributions to knowledge, this hospital has developed many physicians who have later become professors of medicine, here and abroad, and who have carried the spirit of scientific investigation into many medical clinics, and have influenced many students of medicine.

The influence of Dr. Flexner on Public Health has also been of much significance. Through his connection with the Rockefeller Foundation, he was interested in the work of the International Health Division, and when that organization established laboratories for the investigation of problems relating to its work, these laboratories were located in the buildings of the Institute. Dr. Flexner greatly aided in the activities of these laboratories by his support and advice, and they have been instrumental, not only in improving the scientific attitude of those engaged in public health work, but they have made contributions of great practical importance, as, for instance, concerning the nature and prevention of yellow fever. Dr. Flexner was a member of the Public Health Council of New York State from its foundation, and in recent years served as its chairman. He thus exerted an influence on the more immediate and practical problems of public health work. In later years he himself conducted experimental studies concerning the nature of the epidemic occurrence and spread of disease.

In 1903, Dr. Flexner married Helen Whitall Thomas of Baltimore, a sister of Mary Thomas, President of Bryn Mawr University, in which institution Mrs. Flexner had previous to her marriage been a teacher of English. Her knowledge of English literature and her fine taste and

literary ability were undoubtedly of much influence in widening the interest of Dr. Flexner in literature and the humanities. He became a cultivated speaker, and his scientific writings have great simplicity, clarity and accuracy. From 1905 to the time of his death, he was the editor of the Journal of Experimental Medicine. Under his editorship it maintained the high, almost meticulous, standards of its first editor, Dr. Welch. Following his retirement, Dr. Flexner, with his son, James, published a biography of Dr. Welch, which has great literary excellence, and is not only an authoritative account of his life, but it is a sincere tribute to the man who as long as he lived was Dr. Flexner's "guide, councilor and friend."

During the life time of Dr. Flexner, knowledge concerning disease has increased at a rate never before equaled. To this advance, the United States has now become probably the largest contributor, whereas previously, it contributed comparatively little. It is, of course, impossible to say for exactly how much of this change Dr. Flexner has been responsible. Certain it is that he has been one of the most important figures in this development. With the exception of Dr. Welch, probably no single man has played so important a part in the advance of scientific medicine, and with it the improvement in medical education and practice in this country. There is no doubt that the Rockefeller Institute has been of great importance. For this, Dr. Flexner is in great part responsible. Although his name is not inscribed over the portal, it is his monument.

RUFUS COLE

*Summary and Recommendations of Report on Planned Parenthood Clinics by the Committee on Public Health Relations of The New York Academy of Medicine**

I—SUMMARY

In Greater New York there are above 28 organized places where a woman may apply for contraceptive advice, instruction, and the necessary supplies. These may be classified as follows:

1. Special contraceptive hospital clinic departments.
2. Hospital gynecological clinics.
3. The Margaret Sanger Research Bureau. (Affiliated with the Planned Parenthood Federation of America, Inc.)
4. Planned Parenthood Committee of Mothers' Health Centers, and coöperating Maternal Health Centers—Kings County Planned Parenthood Committee, Staten Island Committee for Planned Parenthood, Far Rockaway Mothers' Health Center Committee, and Planned Parenthood Committee of Jamaica, all affiliated with the Planned Parenthood Federation of America, Inc.
5. Two independent organizations: The Judson Health Center, and the International Workers Order Birth Control Clinic.

A summary of the organization and work of these clinics and centers is herewith presented:

Special Contraceptive Hospital Clinic Departments—There are only 5 hospitals in Greater New York in which contraceptive advice is given in a separate department. These departments are well housed, and their work measures up to fair clinical standards. Considering the great demand for contraceptive advice and the large area from which these hospitals draw patients, the number of women served is very small.

Hospital Gynecological Clinics—The hospital gynecological clinics giving contraceptive service have no separate records for contraceptive work. Consequently there is no way of telling, without going over every record in the clinic, the number of women taken care of, the type and character of the work done, and the results.

In some of the gynecological and postpartum hospital clinics the work is done sub rosa, and therefore no records are kept.

The Margaret Sanger Research Bureau—This is the best equipped and largest center in Greater New York. It is the leader in the contraceptive work done in the city. It sets the example for all the extramural centers, and a great majority of the physicians now in charge of contraceptive clinics have had their training at the Bureau.

The Planned Parenthood and Maternal Health Centers—With the exception of the newly established Harlem Center, these centers are usually located in settlement houses, or in improvised locations, where the facilities for proper type of work are limited. The waiting rooms are crowded, and in some places they are in hallways, without any provision for the patients' comfort. Both new and old patients attend on the same day. Under such a plan, the centers are crowded, and patients who return to obtain new material must very often wait unnecessarily long periods of time. The doctors and nurses are constantly hurried in their work.

The Judson Health Center and the International Workers Order Birth Control Clinic—These clinics function independently. Both receive a rather small number of patients. Both have adequate quarters. In one instance the contraceptive clinic is a part of a general health clinic and most of the patients are referred from this clinic. The other is maintained by a labor union and the clientele is largely from among the union members.

Physicians—With the exception of the director of the Margaret Sanger Research

* Approved by the Council of the Academy on Wednesday, March 27, 1946.

Bureau, all the doctors employed in the contraceptive centers are women. The physicians in charge of the Planned Parenthood centers are giving their services for small fees, and many of them are not interested in the underlying medical and social problems. Often, they are not the best physicians obtainable, and their work is frequently superficial. The type of work done at the centers requires a certain amount of teaching ability, tact, and time. To the average patient, the technique of contraception seems strange and complicated, and unless the physician can make herself clearly understood and be patient, the woman may become confused and discouraged. Several of the doctors are foreigners and difficult to understand in ordinary conversation.

Records—The forms and charts used in the centers are furnished by the Planned Parenthood Committees. The social history is usually taken by a volunteer, or, in case the volunteer is absent, by the nurse who has a great many other duties to attend to at the same time. Most of the histories are taken either in an open waiting room or in a small partitioned office; no provision is made for privacy. Questions and answers can be heard by those present in the room. This is not conducive to accurate history taking, or to obtaining information which the patient considers confidential. The personal and family histories taken by the volunteers are however fairly complete. The workers are untrained in handling patients and unfamiliar with the basic principles of social service. They render their services gratuitously, and there is no way of controlling the quality of their work or the regularity of their attendance.

The medical histories often are sketchy and incomplete, either because of the constant pressure of new patients or the carelessness of the physician. The marital histories, which are classified under general physical examination, receive little attention. The follow-up records seem entirely inadequate and of no scientific value. Furthermore, the records are not cross-indexed.

Examination—The physical examination usually is limited to a pelvic examination, which is fairly adequate. Rarely is a record made of a general physical examination.

As most of the physicians are general practitioners, their diagnosis of pelvic abnormalities leaves much to be desired.

Referrals—Whenever an abnormality is found, the patient is referred to her own private physician, if she has one, or to a hospital clinic. No physician is permitted to refer a patient to her own office. Contrary to rumors, there is no evidence that this type of unethical practice is in existence in the Planned Parenthood centers in Greater New York.

Methods Prescribed—The procedure followed in all centers consists of the use of coil-spring type diaphragms and jelly. In complicated cases where a regular vaginal diaphragm will not fit, a special diaphragm or cervical cap is fitted.

Effectiveness of Method—The information obtained in those hospitals where the follow-up is fairly reliable indicates that the method is effective, but that many of the patients tire of the elaborate preparation. A follow-up in one of the hospital clinics, where only those having serious medical indications were given contraceptive advice and told that pregnancy might endanger their lives, showed that only about 70 per cent persevered in the use of the method; 20 to 30 per cent were human failures.

Administrative Practice — The trained nurse is the administrative director of the individual center. She admits the patients, supervises the work of volunteers, gives the lectures and demonstrations, sets up the treatment room, takes care of all the supplies, assists the doctor, collects the fees, and sees that everything is safely stored away. In her spare time, she sends out follow-up cards.

Admission Practice—Admissions at the extramural centers are made almost entirely by the nurse, and very few applicants are turned away. As far as could be learned, only unmarried women are excluded.

Fees—Charges are graduated according to the income and the number of children in the family.

Follow-up—In New York City, the follow-up consists of sending a letter to the patient who has not returned after six months, and visiting the home of the patient if the letters bring no result. In the Brook-

lyn centers because of the scarcity of nurses, no home visits are made. In all centers, if the patient does not return within a year, the case is considered closed.

In short, the Planned Parenthood centers are trying to do an important and necessary work with limited financial resources and without the proper facilities. Such facilities can best be provided by hospital clinics.

II—RECOMMENDATIONS

1. The New York Academy of Medicine, with its traditional interest in the health and welfare of the family and in problems of human fertility, should assume leadership in the recognition of medically indicated contraception as an integral and essential part of preventive medicine.

2. Contraceptive advice should be given by well-trained physicians, both in their offices and in hospital clinics, only when on the basis of a thorough medical study, they are professionally and morally satisfied that such action is justified. Child-spacing should be recognized as a medical indication.

3. The New York Academy of Medicine should declare itself in favor of including the teaching of indications, and the training in techniques of contraception, in medical college curricula, and of providing facilities for postgraduate education of interns, residents, and other physicians.

4. Inasmuch as family-planning advice is a health service, private physicians and hospitals, as well as the proper health authorities, should assume the responsibility of providing it.

5. When contraceptive services have become a recognized part of hospital service in the city, the Planned Parenthood centers should confine themselves to the education of the public, and all education should be under medical supervision.

6. The educational program of the Planned Parenthood Federation toward fertility should take a positive attitude as well as a negative one. Contraceptive advice in the centers operated by Planned Parenthood organizations should not be given to anyone who may apply for it, but every effort should be made to analyze each individual situation and to urge parenthood strongly, where the conditions warrant it.

7. Until such time as the hospital clinics take over contraceptive clinic service, the Planned Parenthood organizations should continue to maintain contraceptive centers which conform to standards set up for licensure of dispensaries by the State Board of Social Welfare, and The New York Academy of Medicine should strongly urge upon that Board that these centers be licensed, because they are an important part of preventive medicine and because they cannot be otherwise controlled.

8. Centers so licensed should conform to the following criteria:

a. They should have adequate financial support to provide good service and proper staff.

b. Only physicians well trained in this special work and interested in the medical objectives of contraception should be employed.

c. Only nurses who are interested in contraceptive services as a part of maternal health, and who have an understanding of public health and social service procedures, should be employed.

d. New cases should be accepted by appointment only, and the number of patients limited, so that the physician and nurse may give the attention each requires. The optimum patient load per physician and nurse should be determined and maintained. Clinics should be held at hours most convenient to the patients.

e. New patients should be given a general physical examination at the centers, or elsewhere if this is impossible there, and all the findings should be recorded. Adequate pelvic examinations should be made at the centers.

f. The patient's reasons for requesting contraceptive advice should be investigated by the physician and clearly stated on the chart, together with the doctor's reasons for giving such services.

g. Patients who seem to have difficulty with the recommended method of contraception or who find it too complicated, should be given some simpler method, which, while not so effective, would probably be used more consistently for a longer period.

h. The clinic physician should be trained to look for and recognize abnormalities, and

should impress upon the patients the need of proper medical care of such conditions.

i. Patients with psychological maladjustments or social problems should be referred to a proper accredited agency or clinic.

j. There should be periodic reviews of standards, and supervision of the work of the physicians in the centers, by competent boards of medical consultants.

k. Periodic conferences of clinical staffs should be required.

l. Adequate records, with a strict follow-up, should be kept as well as statistics for future studies.

m. The waiting rooms should be clean and comfortable; the history taking and consultation rooms should afford privacy; and dressing and toilet facilities should be accessible to the examining rooms.

n. Clerks and volunteers should be given instruction and guidance in the underlying principles of social service. In the larger centers there should be a professional medical social worker.

Required Readjustments—Unless present unsuitable conditions in the settlement house centers can be improved, the family-planning centers located there should be moved to more suitable independent quarters.

Those extramural centers which are below minimum standards should be discontinued.

The Lenox Hill Hospital and the new Hannah Stone Memorial Center in Harlem should serve as patterns for hospital clinics and extramural centers.

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("Possession does not imply approval.")

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